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Cardiac manifestations of myasthenia gravis: A systematic review

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ABSTRACT

Introduction: Myasthenia gravis is an autoimmune disorder targeting skeletal muscles. Striated cardiac muscle can be a target for immune attack manifesting as heart failure, arrhythmia, and sudden death. We aimed to review cardiac manifestations of myasthenia gravis, its underlying pathogenesis and clinical relevance.
Method: We searched literature published from 2003 to 2013 on cardiac involvement in myasthenia gravis using PubMed, Scopus and Ovid databases using the terms 'heart failure'; 'cardiomyopathy'; 'myocarditis'; 'arrhythmia'; 'coronary'; 'heart' and 'myasthenia gravis'. Forty-one articles were chosen comprising of 29 case reports, 4 review articles and 8 retrospective/prospective studies.
Result: Fifteen percent of myasthenia cases had thymoma. Most of them (97%) had antibodies against striated muscle (anti-titin, anti-ryanodine and anti-Kv 1.4 antibodies). Older age, severe myasthenia and myocarditis appeared to be associated with anti-striational antibodies. Takotsubo cardiomyopathy was the most commonly reported cardiomyopathy. Giant cell myocarditis was a rare but fatal manifestation associated with striational antibodies however in-vitro study failed to produce their cytotoxic effects. T wave changes, QT prolongation, anticholinesterase induced atrioventricular block and sudden death were less commonly reported. Abnormal vasoconstrictive coronary response to acetylcholine, development of pericarditis and cardiac surgery leading to myasthenia gravis has been reported.
Conclusion: Heart muscle is a target for autoimmune inflammation in myasthenia gravis. Advancing age, thymoma, and anti-Kv1 antibodies appeared to be risk factors. Symptom overlap with myasthenia may result in failure to recognize cardiac involvement. Prospective studies are needed to establish causal link with striational antibodies and to make screening recommendations for cardiac involvement.

1. Introduction

Myasthenia gravis (MG) is a neuromuscular autoimmune disease. Antibodies to nicotine acetylcholine receptors (AChR) at the neuromuscular junction cause defective neuromuscular transmission in skeletal muscles that manifests as muscle weakness [1]. Myasthenia is known to involve other body systems including the heart. MG patients have a higher prevalence of cardiac manifestations in the presence of thymoma (10–15%) [1]. The article reviews literature on cardiomyopathy, heart failure, arrhythmias, coronary and valvular disease in MG.

2. Methods

We searched PubMed, Scopus and Ovid databases for articles in English from 2003 to 2013. We found 94 articles for 'myasthenia' and 'heart', 47 for 'cardiomyopathy', 27 for 'arrhythmias', 17 for 'heart failure', 17 for 'coronary disease', 12 for 'valve disease', 30 for 'myocarditis' and 5 for 'pericarditis'. We found 249 articles, 41 of which were selected for review based on relevance to the topic. Among the 41 articles, 29 were case reports, 4 review articles, 5 case–control/retrospective studies, one in-vitro study and two were prospective studies.

3. Result and discussion

3.1. Anti-cardiac antibodies

AChR antibodies specific to skeletal muscles do not bind to heart muscle [2]. Forty-eight percent of all MG cases and 97% of all thymoma associated MG, have antibodies towards heart muscle [1,3]. Along with AChR antibodies, thymoma patients exhibit abnormal humoral response with anti-striational antibodies, anti-muscle specific tyrosine

Abbreviations: MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle specific kinase; VGCC, voltage gated calcium channel; RyR, ryanodine receptor; ECG, electrocardiogram; AV, atrioventricular; GCM, giant cell myocarditis; BP, blood pressure; TNF, tumor necrosis factor.

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kinase (anti-MuSK), anti-voltage gated calcium channel (anti-VGCC) antibodies, antibodies against beta-adrenergic receptors and abnormal T cell mediated immunity [3]. Anti-titin, anti-ryanodine receptor antibodies (anti-RyR) and anti-Kv 1.4 antibodies (KCNA4 antibodies) [4], collectively called anti-striational antibodies are commonly reported in MG cases having cardiac involvement [1,5]. Titin is a giant protein in the skeletal and cardiac sarcomere. The immunogenic region of titin called MG titin-30 is situated near the A/I-band junction [6]. RyR is a calcium release channel located in the sarcoplasmic reticulum with important role in regulating the excitation contraction coupling through calcium release [1]. Kv 1.4 is a voltage gated potassium channel. Anti-titin antibody is detected in 20–40%, anti-RyR in 13–38% and anti-Kv 1.4 in 12–15% of MG cases [6]. Complement activation by striational antibodies and T cell proliferative response have been reported [3,6] without proven clinical significance. In non-MG patients, autoantibody to beta 1 adrenergic receptor has been associated with dilated cardiomyopathy [7].

Myocarditis developed in 37.5% MG patients with anti-striational antibodies [5]. On immunological evaluation ($n = 8$), anti-titin, anti-RyR and anti-Kv1.4 antibodies were present in 63%, 75% and 75% cases respectively. Immunomodulatory treatment benefitted all. Among those with myocarditis, heart failure and arrhythmias developed from 13 to 211 months after the onset of MG. Histological evaluation showed widespread inflammatory infiltrates containing multi-nucleated giant cells and myocardial degeneration with varying severities [5]. However, an in-vitro study failed to show morphological changes or cytotoxic effects in human derived heart muscle cells by MG sera when compared to healthy human sera [1].

Anti-Kv 1.4 antibody may be a potential marker for the development of lethal autoimmune myocarditis [5,6]. A large study involving 650 MG patients showed an incidence of 10.8% for anti-Kv 1.4 antibodies. Sixty percent of them had abnormal electrocardiogram (ECG) [2]. Ultrasound echocardiography of ex-vivo chick embryos exposed to these antibodies showed significant suppression of heart muscle function. Anti-Kv 1.4 antibody has also been associated with QTc prolongation, lethal arrhythmias including ventricular tachycardia, sick sinus syndrome, complete atrial ventricular (AV) block, severe myocarditis, and sudden death [2,6,8].

Currently, data that strongly supports pathogenic role of these antibodies is lacking, however, they may influence cardiac function by complement activation and T cell proliferation.

3.2. Heart failure and cardiomyopathy in MG

Giant cell myocarditis (GCM) and Takotsubo cardiomyopathy have been associated with MG. GCM is often fatal while Takotsubo cardiomyopathy is reversible. Interestingly, both have very different pathogenesis.

2A: GCM is a severe form of myocarditis with myonecrosis and serpiginous infiltrate of chronic inflammatory cells including giant cells. Twenty-two cases of GCM with thymoma and 12 autopsy cases of MG with thymoma, polymyositis and myocarditis have been reported [9,10]. Giant cells were found in 50% cases in both myocardium and skeletal muscles [10].

CD3, CD68, CD20 and CD8 positive giant lymphocytes were found in myocardium and skeletal muscles of a 68 year old with MG after she developed myocarditis [11]. GCM occurred in a 72 year old patient with MG on azathioprine with no specific correlation between areas of inflammation and IgG deposits on immunohistochemistry [9]. Both cases had thymoma. There are two cases of GCM reported shortly (7 to 10 days) following thymoma resection with one showing CD3 lymphocytes, CD68 histiocytes and giant cells [12]. Autopsy proven myocarditis occurred in a case of stage IVa thymoma with positive AChR antibody titers but without clinical MG following chemotherapy [10]. Two cases of invasive thymoma developing GCM and myositis were also reported [13,14]. All cases were fatal. Asymptomatic GCM in a patient with MG with strongly positive striational antibodies was eventually fatal [15].

Pathogenesis of GCM: Inflammation during muscle degeneration activates myogenesis. Mononucleated myoblasts are induced, that fuse to form multinucleated myocytes [11]. The etiology of inflammation is unclear and GCM is not specific to MG. Inflammatory chemotactic factors may attract macrophages that fuse with each other during endocytosis and form giant cells [11]. GCM has been reported in other autoimmune disorders including Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus etc. [11]. Risk factors for GCM include increased age and thymoma.

2B: Stress induced cardiomyopathy i.e. Takotsubo cardiomyopathy is a transient reversible form of left ventricular dysfunction often presenting as acute coronary syndrome in the absence of significant coronary stenosis. It is precipitated by emotional or physical form of stress which causes a catecholamine surge [16] resulting in suppressed myocardial function. Animal models have demonstrated transient hypocontraction of cardiac muscle upon exposure to high levels of catecholamines [17].

MG can precipitate severe stress particularly during a crisis episode [17–22]. Takotsubo cardiomyopathy developed in patients on plasmapheresis and intravenous immunoglobulin during myasthenia crisis [17,18,20–22]. A case of heart failure with difficulty weaning the patient off the ventilator despite aggressive therapy was retrospectively diagnosed to have myasthenia crisis [19]. Recurrent Takotsubo cardiomyopathy occurred with every episode of myasthenia crisis in an elderly female [23]. MG and cardiomyopathy developed concurrently in a 68 year-old 4 weeks after mitral valve replacement. There was no association with thymoma and all cases were related to myasthenia crisis.

In conclusion, older patients with severe MG appear to be at a higher risk for developing stress-induced cardiomyopathy. GCM was seen more often in elderly cases with thymoma and was often fatal. Routine testing of striational antibodies is not currently indicated as no large prospective study has proved its association with MG.

A case–control study analyzed left ventricular long-axis function in MG [7]. Tissue Doppler imaging was used in 22 MG patients along with 22 matched controls before and after pyridostigmine. Tissue velocities were analyzed at systole (S′), early (E′) and late (A′) diastole. Peak systolic strain was analyzed at the time of aortic valve closure. MG patients had a significantly higher systolic and diastolic blood pressure (BP) than controls ($p = 0.007$ and 0.017 respectively). Systolic BP remained high after pyridostigmine ($p = 0.009$). Mean early diastolic AV-plane velocity detects changes in left ventricular diastolic function, which is undetectable by measurement of ejection fraction. It was significantly lower in patients than controls (7.7 cm/s versus 9 cm/s, $p = 0.0036$) before pyridostigmine. This effect disappeared after pyridostigmine. Before pyridostigmine, S′ and E′ were lower in MG patients but without statistical significance. Patients had a lower peak systolic strain than controls (−18.8% versus −21.6%, $p = 0.011$). This study suggested a pyridostigmine responsive decreased left ventricular function. Systolic BP was a significant determinant for difference in the two groups as these effects disappeared after adjusting for same [7].

3.3. Myasthenia gravis and pericarditis

Two cases of constrictive pericarditis post-irradiation for invasive thymoma were reported [24]. A case of transudative pericardial effusion and atrial flutter with AV block that resolved with plasmapheresis and immunosuppressive therapy was reported [25]. Radiation treatment for thymoma may increase risk for pericarditis.

3.4. Myasthenia gravis and arrhythmias

Available literature is based on analysis of electrocardiograms (ECG) of MG patients. Sudden cardiac deaths have been reported but no definite association has been discovered. Fluctuations in heart rate is mostly due to autonomic dysfunction and less so due to pathology of conduction system itself. Hence, we will review autonomic function in MG.